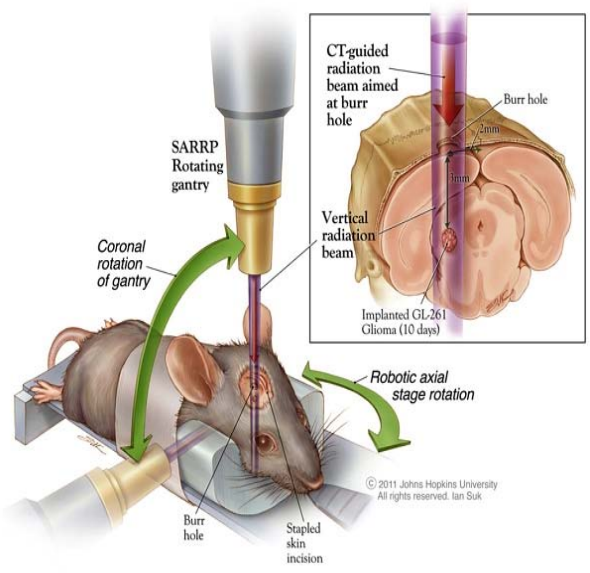
protocols under experimental conditions. Our laboratory is developing an in vivo radiobiology research program using the small animal radiotherapy research platform (SARRP, Xstrahl Life Sciences) as a central enabling technology to perform translational studies focussing on biologically optimised radiotherapy, nanoparticle theranostics and novel combination treatments. A major challenge now facing investigators is how to correctly apply the technology to accurately model clinical scenarios in relevant small animal models so that it can be exploited to its full potential in driving translational studies with outcomes likely to impact current standard of care in radiation oncology.
An overview of the current state-of-the-art in preclinical radiotherapy will be presented including recent developments such as integration of bioluminescence imaging, preclinical 4-D CBCT and Monte Carlo based dose calculation methods. Examples of innovative preclinical studies will be highlighted along with experience from our own laboratory from commissioning to experimental design and important considerations for the successful execution of hypothesis-driven investigations using small animal radiotherapy.
Despite certain challenges, small animal radiotherapy has much potential to bridge the translational gap between basic radiobiology and radiotherapy. As the technology develops and investigators gain experience as multidisciplinary scientists, pre-clinical studies that increasingly replicate the clinical scenario will drive new approaches in radiobiology that should ultimately translate to human health gains.

SP-0505
Radiation biology studies with a small animal irradiator: results from the Research Programme at Johns Hopkins University
P. Tran[1]
[1]*Johns Hopkins University The Sidney Kimmel Comprehensive Cancer Center, Department of Radiation Oncology, Baltimore, USA*

Although advances with in-vitro cancer cell culture models have occurred recently, in vivo tumor models are still crucial for the study of novel radiation treatments. This is particularly important for radiation combination approaches that target tumor cell non-autonomous anti-cancer pathways such as the tumor microenvironment or the immune system. In addition, more sophisticated animal studies with radiation are now possible with the advent of technologies that integrate treatment planning, imaging, and radiation delivery capabilities such as with the small-animal radiation platform (SARRP; Fig 1).



Tumor xenograft models using human-derived tumor models implanted into immune-deficient mice are a mainstay of pre-clinical testing and discovery. Although the majority of in vivo studies involve immunocompromised mice, such as athymic, severe combined immune-deficiency (SCID) or NOD-SCID mice, these models are less ideal with radiation studies because some of these mice have mutations in DNA response and repair pathways. The abnormal DNA repair mechanisms in these mice limit the applicability of results with radiosensitizers given the integral role of DNA damage to the biologic effect of radiation therapy. Furthermore, anti-tumor effects of radiation may be mediated by the immune system. As a result of these limitations, genetically engineered mouse models (GEMMs) are becoming more widely used in preclinical studies with and without radiation. “Co-clinical trials” that use GEMMs that faithfully replicate the mutational events observed in human cancers to conduct preclinical trials that parallel ongoing human phase I/II clinical trials have shown great promise in cancer. This presentation will review published and on-going pre-clinical studies targeting both cancer cell autonomous and cancer cell non-autonomous pathways utilizing the SARRP with both xenograft tumor models and GEMMs at Johns Hopkins.

SP-0506
How do we select meaningful pre-clinical models for studies in radiation biology?
D. De Ruysscher[1]
[1]*MAASTRO clinic, Radiation Oncology, Maastricht, The Netherlands*

Clinical research faces many problems, of which the availability of pre-clinical models that predict the human situation is one of the most important. Pre-clinical tumour models are being used for decades in many cases with the assumption that they are predictive for what will later happen in humans. As such, the use of pre-clinical, mostly mouse, models may limit the exposure of inactive and or toxic treatments in patients. Although there is no doubt that pre-clinical models have been crucial to understand better molecular and other characteristics of carcinogenesis, growth and metastases and were the basis of many currently used cancer therapies, they still have considerable shortcomings. Classical mouse models use tumour cell lines that have been grown in vitro for many years and hence may have altered characteristics compared to *de novo* tumours. These tumour cells are then implanted subcutaneously in mice and tend to grow rapidly and thus do not mimic the much slower doubling times of most human cancers. This faster tumour growth may lead to a higher sensitivity for most chemotherapy drugs and hence erroneous conclusions. Moreover, in some situations, ectopic (out of the normal place) subcutaneously implanted tumours — still a standard methodology — may respond differently to treatment compared to tumours grown in an orthotopic site, i.e. in their organ or tissue of origin, such as breast cancers in mammary fat pads. The latter may correspond more to the human situation. Moreover, metastases frequently show other responses than primary tumours in patients, and it is only recently that these effects can be mimicked in genetically engineered mouse models. Tumour bearing mice are often treated with drugs at levels, or with pharmacokinetics, that are not relevant to humans. Furthermore, nearly all pre-clinical models have not used tumours that were pre-exposed to another therapy, whereas in many phase I and phase II clinical trials only patients that show tumour progression after one or more systemic treatments are included. With the huge interest in immune therapy, the use of humanised mice has gained even more attention than before. However, these models still face problems with remaining mouse innate immunity and weak human innate and adaptive immunity. Even the best models suffer from the development of wasting disease in highly engrafted humanized mice and poorly developed lymph nodes and germinal centres. It is also unclear if the cell trafficking resembles that of humans.At present, no single mouse models mimics perfectly the human situation. However, models that use injected tumour cells in the organ from which they were derived and which form metastases in organs that are similar to the human situation may be the most appropriate for they bear a micro-environment that resembles that of humans.